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Multiscale Modeling of Nano-scale Phenomena: Towards a Multiphysics Simulation Capability for Design and Optimization of Sensor Systems

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December 3, 2003

This work was performed under the auspices of the U.S. Department of Energy by University of California, Lawrence Livermore National Laboratory under Contract W-7405-Eng-48.

MULTISCALE MODELING OF NANO-SCALE PHENOMENA:

Towards a Multiphysics Simulation Capability for Design and Optimization of Sensor Systems

A Multidirectorate White Paper

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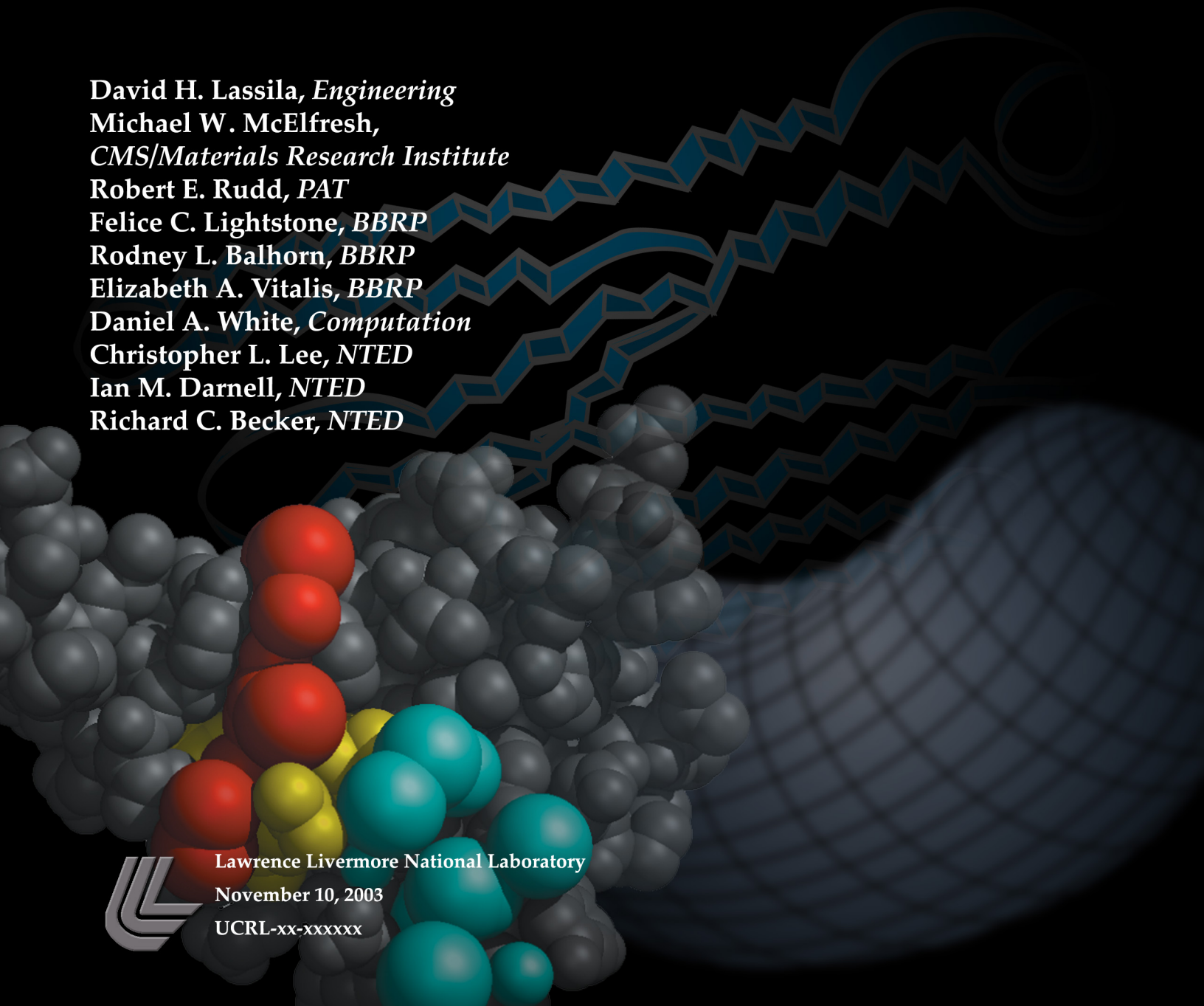

Lawrence Livermore National Laboratory
November 10, 2003
UCRL-xx-xxxxxx

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Lawrence Livermore National Laboratory
July 24, 2003

Executive Summary

In this white paper, a road map is presented to establish a multiphysics simulation capability for the design and optimization of sensor systems that incorporate nanomaterials and technologies. The Engineering Directorate's solid/fluid mechanics and electromagnetic computer codes will play an important role in both multiscale modeling and integration of required physics issues to achieve a baseline simulation capability. Molecular dynamic simulations performed primarily in the BBRP, CMS and PAT directorates, will provide information for the construction of multiscale models. All of the theoretical developments will require closely coupled experimental work to develop material models and validate simulations. The plan is synergistic and complimentary with the Laboratory's emerging core competency of multiscale modeling. The first application of the multiphysics computer code is the simulation of a "simple" biological system (protein recognition utilizing synthesized ligands) that has a broad range of applications including detection of biological threats, presymptomatic detection of illnesses, and drug therapy.

While the overall goal is to establish a simulation capability, the near-term work is mainly focused on 1) multiscale modeling, i.e., the development of "continuum" representations of nanostructures based on information from molecular dynamics simulations and 2) experiments for model development and validation. A list of LDRD-ER proposals and ongoing projects that could be coordinated to achieve these near-term objectives and demonstrate the feasibility and utility of a multiphysics simulation capability is given*.

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*The contents of this white paper are primarily the result of a series of roundtable discussions on sensor technology, chemical and biological threats, nanomaterials, biological experiments and multiphysics computer code simulations. The authors gratefully acknowledge the participation of all of the people that contributed to these discussions, as listed in Appendix A.

1. Introduction

Over the last 10 years, there has been a rapid increase in the number of studies of nano-scale phenomena using atomistic simulations. For example, molecular dynamics (MD) simulations have been performed to study the structure and properties of DNA, carbon nanotubes and many other nanomaterials. In these simulations each individual atom is resolved and an interatomic potential is used to represent the binding that holds the collection of atoms together as a solid. These simulations model material behavior over relatively short periods of time, because each atom needs to be resolved in terms of position while it is vibrating at the Einstein or oscillation frequency, which results in time steps on the order of 10^{-15} s^{-1}. This typically constrains MD simulations to modeling of material behavior over time frames that are at most on the order of 1 to 10 ns. While a great deal of information can be gleaned from atomistic simulations, the inherently small time-step limits our ability to model many important phenomena that occur over much larger time scales.

Multiscale modeling via information passing has proven to be useful in the transition of information generated by atomistic simulations to "continuum" models that allow **larger systems** to be simulated over **greater periods of time**. An example of multiscale modeling methodology is shown in Figure 1, where the information on the mechanical behavior of DNA is generated using atomistics, and subsequently used to construct a continuum model. This potentially allows for realistic multiphysics simulations of the DNA molecule in a system that is being developed for purification of DNA samples.

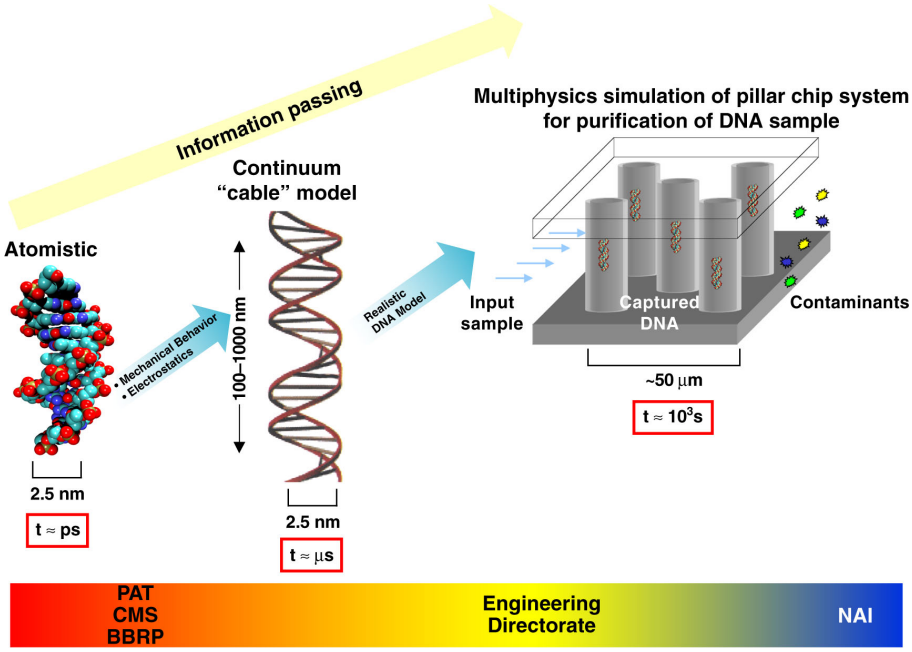

Figure 1. The multiscale modeling methodology using "information passing" is illustrated for a DNA strand, where the cable model represents sections of atoms. Using the "cable" model for DNA it is possible to then perform a multiphysics simulation for design and optimization of a "pillar chip" used to purify DNA samples (C. Lee, K. Ness).

In this white paper, we outline an effort to create a multiphysics simulation capability for the design and optimization of biosensors that incorporate nanomaterials. In the following sections we attempt to answer these questions:

- What simulation tools will future "sensor designers" use?
- What are nanomaterials?
- How will next-generation sensors incorporate nanomaterials?
- What is the near-term target for a multiphysics simulation?
- What multiscale modeling efforts are needed to establish the near-term simulation?
- What experiments need to be performed to support the multiscale modeling?
- What FY-04 work (on-going and proposed) can tie in with the overall plan?

Given the grand challenge that creating a multiphysics simulation capability presents, the answers to these questions will likely evolve as will specific work plans. However, it is clear we must begin these efforts if we are to establish a "first" simulation capability for design and optimization of sensors that incorporate nanomaterials and technologies.

2. Sensor Designer

One can draw an analogy between the multiphysics computer code simulations that are used for the stockpile stewardship mission and what could be created to enable future "sensor designers" to take advantage of phenomena unique to nanomaterials in the design and optimization of sensor systems. Within the Lab's A and B Divisions, the term "designer" is used to describe the staff members that use 3D computer codes to simulate the performance, safety and aging effects of stockpile weapon systems. Large "code development" teams consisting primarily of physicists, engineers and computer scientists create these simulation capabilities. The codes are typically very large (100,000s lines of coding) and can account for the collective effects of a wide variety of materials behavior including, radiation transport, high-pressure compression, material strength and failure properties. These codes are designed to run efficiently on state of the art ASCI parallel super computers. Our ability to handle large problems in terms of discretized elements or zones is ever increasing, giving designers more resolution of important details previously overlooked. Naturally, the simulations are only as good as the materials models used, and recently the DNT "Dynamics of Metals" Program's multiscale modeling efforts are an integral part of the efforts to improve the predictive capability of material strength and failure models. The combined Lab-wide investment, including computing hardware and maintenance, is in the range of $100M/year and gives the "weapon designer" unprecedented simulation capabilities.

The development and fielding of better sensing capabilities are part of the Lab's evolving national security mission. Currently sensors are designed and refined mainly by an Edisonian approach with little or no supporting multiphysics computer code simulations. Clearly LLNL has had many successes in the area of sensor design without the advantages of having a multiphysics simulation capability. However, if "sensor designers" were able to employ large multiphysics computer codes analogous to the weapons codes used in A and B Divisions, the design process would certainly involve:

1) **more creativity -** because of the ever increasing number of design possibilities that incorporate "nanomaterials" and technologies could be explored, and

2) **faster and less costly design optimization efforts -** because simulations could be performed in a small fraction of the time needed to prove out a design via prototype fabrication and testing.

The development of multiphysics simulation capability for the design and optimization of sensors would clearly be of great benefit and would in essence create a new career path at LLNL, i.e., a "sensor designer" (who might sit in the Lab's NAI directorate). LLNL is well positioned to create this simulation capability because it would leverage much of the ongoing investment in stockpile stewardship simulation capabilities, e.g., the NNSA/DNT Terascale Simulation Facility and many of the cutting edge computational techniques developed within the Computations Directorate for running codes on massively parallel processing computers. However, as we will show, the main challenge in establishing a simulation capability for sensor design is the representation of material behavior that is unique to the nanometer length scale in an integrated multiphysics computer code.

3. What are Nanomaterials?

Nanomaterials are roughly defined as solids with characteristic dimensions that are 200nm or less. Perhaps the most classic example is carbon nanotubes, as shown in Figure 2. Other newly invented nano-materials include, self assembled monolayers (SAM), sol-gel derived particles, and various composite materials that incorporate nanomaterials in their structure. Biological molecules such as DNA strands and proteins also fit within the definition of "nano-materials" and are sometimes referred to as "soft" nanomaterials. In fact, it is the relative similarity in size that makes the employment of "hard" man-made nanomaterials advantageous in the design of sensors to detect biological agents.

The properties of nanomaterials are frequently very different than typical engineering properties (as shown by numerous MD simulation results and experiments). For example, carbon nanotubes have extremely high specific strength properties and demonstrate the ability to be electrically conductive, semiconductive and insulating depending on their orientation and environment. In addition to unusual "engineering properties" some nanomaterials such as Si and CdSe "quantum dots" have unique

photonic and electronic properties. In essence, it is the very small dimensions and concurrent surface-area to volume ratio of the nanomaterials that give rise to these properties and make them inherently very different than traditional engineering materials.

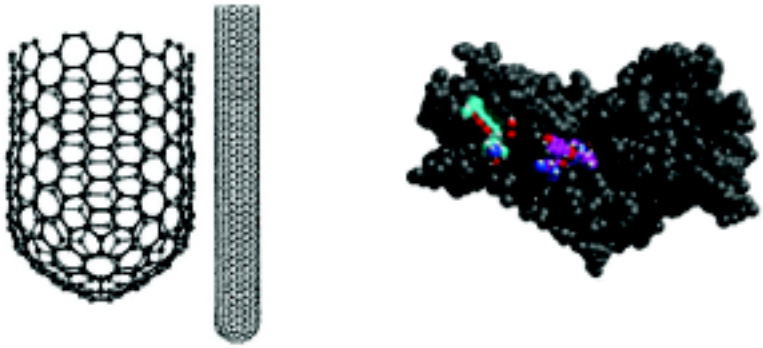

Figure 2. a) Carbon nanotubes are classic examples of a "hard" nanomaterial. b) proteins are sometimes referred to as "soft" nanomaterials, but were of course discovered long before the term "nanoscience" was coined. Nanomaterials are roughly defined as solids with dimensions on the order of 200 nm or less.

4. Nanomaterials and next-generation sensor systems

Nanomaterials have the potential to revolutionize capabilities to sense the presence of biological threats because of their inherent likeness in length scale. It is envisioned that next-generation sensor systems will incorporate a wide variety of nano-materials technologies and will eventually replace many of the current detection technologies that are relatively slow and expensive. Next-generation sensor systems will in some ways resemble "smoke detectors" and will likely be integrated with heating/cooling systems and the Internet. Design goals include;

- real-time information on the presence of threats
- low cost for broad and abundant applications
- capable of detecting multiple threats simultaneously
- robust and reliable in changeable environments
- small and non-intrusive with low power requirements.

There are several sensor detection mechanisms that have been explored that have potential to meet these design goals. Examples of methods that are showing great promise are Surface Acoustic Wave (SAW) devices, microcantilever beams, and Total Internal Reflection Fluorescence (TIRF) methods. The utility of relatively inexpensive functionalized Si microcantilever beams as miniaturized sensors for radiation and chem/bio agents has been demonstrated by many research groups including those headed by Dr. Tomas Thundat at ORNL and Prof Dr. Christoph Gerber at the University of Basel Switzerland. The detection of a chemical or biological agent can be based on either the change of the mechanical resonance or the deflection of the cantilever beam when the

agent attaches to it via chemisorption and/or physisorption. Bonding (chemical and mechanical) is one of the nano-materials aspects of the detection scheme; the beam needs to be "functionalized" with a self-assembled monolayer to attract and retain only the agent being sought. Also, in the "resonance" mode of detection very small beams with dimensions on the order of 10 to 100 nm might be employed to achieve high sensitivity (for example the presence of a single protein). It is important to point out that while the utility of microcantilever sensing has been shown in laboratory experiments, the "smoke detector" goal is still illusive for various reasons, one being the inability to design a robust detection system. The availability of multiphysics simulation capability would clearly accelerate the transition of this and other promising techniques to sensor systems applied in the field.

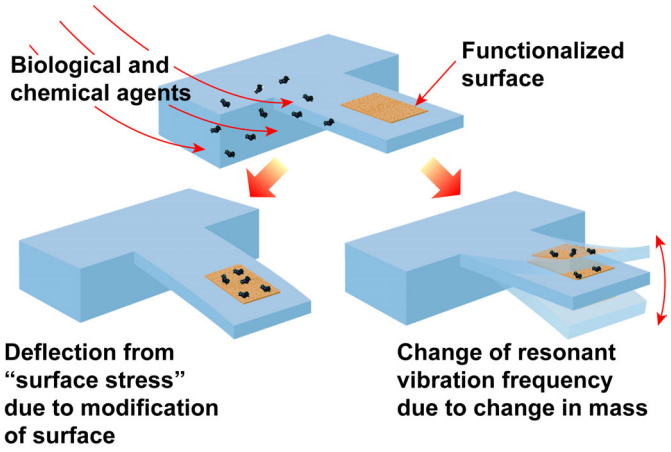

Figure 3. Microcantilever based sensing techniques have been demonstrated to have utility in detection of a wide variety of chem/bio threats and radiation. A) In the static "deflection mode" a surface stress is generated when a molecule attaches to the functionalized surface. The surface stress results in bending that can be detected by a number of techniques, e.g., deflected laser light or piezoelectric effects. B) In the dynamic mode, the effective mass of the beam is changed when a molecule is captured which results in a change of the resonance frequency of the beam.

The microcantilever beam technique illustrates just one of many current detection schemes that employ nanomaterials, others include:

- the use of engineered proteins in conjunction with lipid bi-layers
- functionalized carbon nanotubes to "trap" molecules and ions
- self assembled monolayers in conjunction with surface acoustic waves (SAW)
- electrophloresis for sample collection and concentration
- nano-porous materials for agent collection and pre-sensor filtering
- various techniques employing quantum dots and photonics.

Given the rapid pace of the development of nanomaterials and technologies by researchers worldwide and the race to develop new low-cost ubiquitous sensors for homeland security, it is neither necessary nor prudent for the LLNL to limit its research to any given area. The goal of the development of a multiphysics computer code for sensor design will ultimately require all available nanomaterial behaviors to be simulated concurrently. However, in the near term we must focus on a very well defined problem so that the feasibility and utility of a multiphysics simulation code can be demonstrated within a 3-year effort. To that end, the work outlined in this white paper will focus on the use of a functionalized cantilever beam for the detection of a specific protein. In the next section, we briefly outline the specifics of the functionalized surface and protein interactions (we return to a discussion of multiscale modeling of the beam in Section 9).

5. The near-term demonstration: SHAL/protein binding

A synthesized high-affinity ligand (SHAL) is a molecular compound that binds strongly and specifically to a target protein. In essence, a SHAL can be thought of as an artificial antibody that has been engineered to be more specific* and have higher affinity** than biologically derived antibodies. An example of a SHAL and target protein is shown in Figure 4.

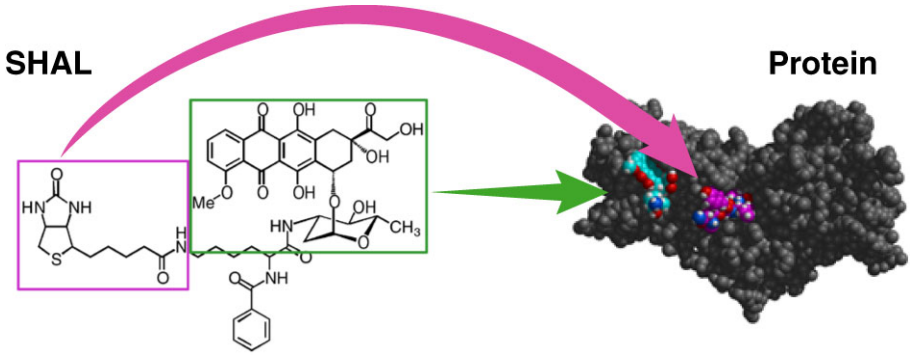

Figure 4. Synthesized high-affinity ligand (SHAL) on the left, and the tetanus toxin protein shown on the right. The SHAL has been engineered and produced at LLNL to bind in two locations on the protein.

(Lightstone, F.C., Prieto, M.C., Singh, A.K., Piqueras, M.C., Whittal, R.M., Knapp, M.S., Balhorn, R. and Roe, D.C. (2000) *The Identification of Novel Small Molecule Ligands that Bind to Tetanus Toxin*. Chem. Res. Toxicol. 13, 356-362 and Cosman, M., Lightstone, F.C., Krishnan, V.V., Zeller, L., Prieto, M.C., Roe, D.C. and Balhorn, R. (2002) *Identification of Novel Small Molecules that Bind to Two Different Sites on the Surface of Tetanus Toxin C Fragment*. Chem. Res. Toxicol.15: 1218-1228.)

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* Highly "specific" SHALs have a low probability of binding to anything except the target protein. **High "affinity" refers to the SHAL's ability to detect very low concentrations of protein (nano-molar range).

Over the past 10 years or so there has been accelerating efforts to produce SHALs for a wide variety of uses including disease diagnosis, prevention, and treatment. More recently, SHALs have been considered for the functionalization of surfaces for detection of biological agents, for example the microcantilever beam shown in Figure 3. The SHAL essentially replaces the use of natural antibodies in this capacity, and there are many significant advantages in doing this, including:

- SHAL is orders of magnitude more specific with higher affinity than antibodies
- Since antibodies are labile (unstable), the SHAL-functionalized surface is more robust and immune to UV and thermal degradation
- SHALs are much smaller than antibodies thus allowing for increased density detection
- the SHAL can be produced easily at a lower cost

The *multivalent* nature of the SHAL is responsible for the high specificity and affinity, i.e., the molecule has more than one binding point on the protein as shown in Figure 4. In designing a SHAL, screening for individual small molecules that bind to the protein is first done computationally and then experimentally. The shape and chemical nature of the individual binders are optimized to bind at specific sites (pockets) on a given protein. This screening process allows a list of effective binders to be easily determined. A bivalent SHAL is produced by linking two selected binders together with a tether molecule (typically polyethylene glycol). The details of designing and experimentally testing a SHAL are quite complex and will not be described further. Rather we cover only the very salient features of the chemical and mechanical nature of the binding that results in the high specificity and affinity of a bivalent SHAL.

The SHAL-protein binding event begins when one of the functional ends of the SHAL is within approximately 1 to 10 nm from its binding location on the protein, as illustrated in Figure 5. Once one end of the SHAL is bound, the effective molarity (concentration) of the other end increases due to the mechanical linkage provided by the tether. Thus, the on-rate increases for the unbound end. Binding is complete when both ends of the SHAL are bound in their respective pockets on the target protein. After binding is complete, it is possible that each end will still have a specific off-rate, but increase in effective molarity significantly increases the observable on-rate, resulting in increased affinity. This is basically how the behavior of two relatively weak molecular binders provide the SHAL very high affinity.

The overall nature of the SHAL/protein binding process as described above is well established. However, the details of some of the important structure-activity relationships are not quantified. For example, the length of the tether molecule has a large affect on affinity, but it is not know (or predicted) what the optimal length should be. Also, other parameters such as the density and arrangement of the SHALs on a substrate will have an effect on the net affinity of the SHALs. It is believed that a simulation of the binding

process, as depicted in Figure 5, would provide insight into both the details of the binding process and information useful in the optimization of various parameters that affect the measured affinity.

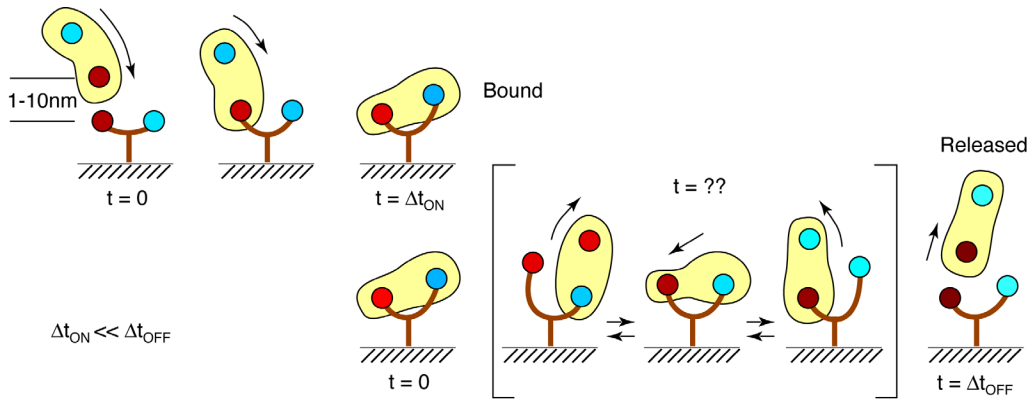

Figure 5. Protein binding to, and releasing from a SHAL. The bivalent nature of the SHAL is responsible for the high specificity and affinity relative to one of the individual binders alone. The mechanisms associated with SHAL binding are complex and involve mechanical, fluidic and electrostatic phenomena.

The simplest experiment involving a divalent SHAL and target protein consists of a buffer solution with a known concentration of target protein (in the micro- or nano-molar range). A plate with SHALs attached to the surface is allowed to bind the protein in solution over a period of time, as depicted in Figure 6. The binding of proteins is measured by a fluorescence technique (or NMR) and recorded. The outcome of the experiments can be represented as a measure of sensitivity relative to the concentration of protein in solution. However, for our modeling purposes data from a typical experiment can be represented as a plot of "binding events" versus time, as illustrated in Figure 6.

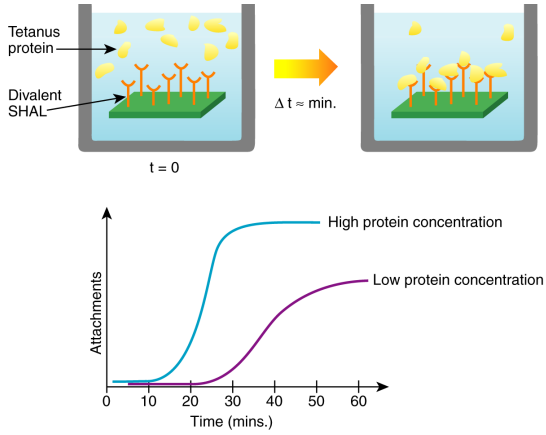

Figure 6. Experiment involving the binding of proteins to SHALs tethered to a plate. The fluid media is a buffer solution (H_2O, sodium phosphate). The data represents the number of binding events increasing and then saturating over a period of time, perhaps on the order of minutes or hours.

Simulation of this experiment will be the near-term goal of work described in this white paper.

One of the near term goals of the multiphysics simulation effort will be to predict the temporal data representing the binding of the SHAL to the protein. This will be a key validation of the multiscale models created for the SHAL and protein that will have all of

the mechanical and chemical bonding physics represented. In achieving a multiphysics simulation capability we expect: 1) a better understanding of the complexities of the actual SHAL/protein binding (Figure 5), and 2) an understanding of the relationship between these complexities and the relatively simple data that results from the SHAL/protein binding experiment shown in Figure 6.

6. Multiscale modeling of the SHAL and protein

While many of the details of the actual binding event are not well known, it is clear from experimental data that the SHAL/protein binding is both chemical and mechanical in nature. The mechanical nature of the SHAL/protein binding is related to: 1) the size and shape of the "binding pockets" on the protein, and the size and shape of the tethered molecules that bind, and 2) the length of the tether that connects the two molecules. The chemical nature of the binding of the two molecules can involve a variety of interactions, including Van der Waals forces (polar forces), the effects of water displacement (hydrophobic/hydrophilic effects), covalent bonds, hydrogen bonds, and other electrostatic phenomena. In this section, we first discuss the application of MD simulations to understanding the SHAL/protein binding; we then discuss "continuum" models that could be developed to model the actual complexities of the binding events.

6.1 Atomistic MD simulations

Some of our understanding of the chemical and mechanical nature of the SHAL/protein binding comes from the results of atomistic MD simulations. In these simulations each individual atom is resolved, and an interatomic potential is used to represent the binding that holds the collection of atoms together as a solid. These simulations model material behavior over relatively short periods of time, because each atom needs to be resolved in terms of position while it is vibrating at the Einstein frequency (on the order of 10^{13} s^{-1}), which results in time steps on the order of 10^{-15} s. This typically constrains MD simulations to modeling of material behavior over time frames that are at most on the order of 1 to 10 ns (some accelerated techniques can extend this, but with some penalties). For the problems of interest here (SHAL and protein), MD simulations have been used to model the shape of the protein at various "equilibrium" configurations. In particular, the MD simulations have been very useful in identifying the best binding pockets on the surface of the protein, both in terms of their shape and chemical nature.

We expect that additional MD simulations would be employed extensively to continue to probe both the mechanical and chemical nature of the SHAL/protein binding. For example, the mechanical compliance of the protein could be studied by imposing appropriate boundary conditions in conjunction with forces to extend/compress/twist/bend the protein. MD simulation would also be needed to further explore the electostatic nature of the protein binding pockets as a function of the morphology of the pockets.

The MD simulations are extremely useful in developing our fundamental understanding. However, the dynamic effects such as the actual binding SHAL/protein event occur over much larger time scale and are fundamentally out of reach of the MD simulation techniques. If we are to simulate the temporal data and complexities of the SHAL/protein binding as shown in Figures 5 and 6, a simulation capability that has a time step on the order of .1 to 10μs will be required (many orders of magnitude greater than the typical MD time step). This is where multiscale modeling and Engineering's solid/fluid mechanics and electromagnetics computer codes come into the picture.

6.2 Continuum models and simulations

Continuum representations of nanomaterials can be performed that, in principle, capture all of the relevant physics over a time frame that is consistent with the experimental observation of binding events (on the order of min.). The multiscale modeling of the SHAL and protein, starting with information from MD simulations and including experimental work is summarized in Figure 7.

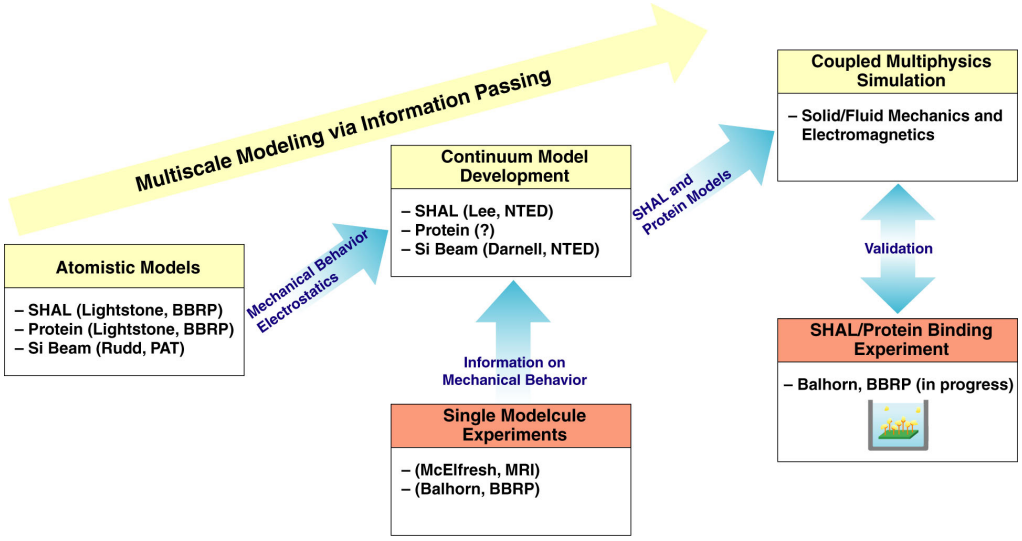

Figure 7. Information pathways for the multiscale modeling of the SHAL and protein, and the multiphysics simulation of the SHAL/protein binding experiment shown in Figure 6.

There are several aspects of the simple SHAL/protein binding experiments that we would hope to recreate with a continuum multiphysics simulation capability that includes both **mechanics/fluidics** and **electrostatics** physics issues. For example, we would like to understand the reasons why the length of the SHAL's tether molecule has a strong effect on binding and determine the optimal tether length that results in the best binding. Also, we would like to study the relationship between the changes in the morphology of the protein binding pockets and mechanical/electrostatic binding forces.

Some simple "continuum" based representation of biological molecules exist, both for the mechanical behavior in a fluid, and also for the chemical (or electrostatic) nature of the binding potential. Currently Engineering is engaged in a research project involving the

development of a simulation capability to model bio-molecules in solution. These simulations are performed using continuum-mechanics-based finite element formulations that can capture the dynamic, structural/mechanical behavior on long (whole molecule) length and (global deformation) time scales. For example, the *mechanical behavior* of a DNA strand represented with "cable" elements is being developed and will be implemented into the ALE3D computer code to allow simulation of biological molecules and fluid/solid interactions as illustrated in Figure 1.

These new "cable" continuum elements could be used to represent both the SHAL and the protein. The mechanical modeling of the SHAL would in principle be straightforward given the fairly simple morphology. However, constructing a continuum model for a protein will be challenging and could take one of several approaches. For example, one might start by considering the modeling of the amino acid groups, as shown in Figure 8 (right). Each amino acid group could be constructed using cable elements and then linked together. This approach would likely involve a very detailed analysis of the forces that "fold" the protein into its compact shape. Another approach would be to model the protein as a continuous media. This could be done with solid "8 node bricks", as illustrated in Figure 8 (left). The constitutive behavior of the brick elements might be similar to that of a compressible hyperelastic media. In the interest of establishing an initial simulation capability, we would choose to construct the mechanical model for the tetanus toxin protein with solid elements.

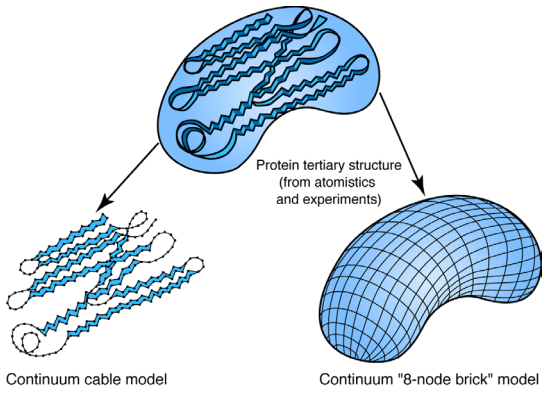

Figure 8. Continuum representations of a protein. The figure on the lower left shows how "cable" elements (as shown in Figure 1), could be used to discretize the amino acid groups. On the right, the protein is shown as solid elements. The constitutive behavior of the solid elements might be similar to compressible hyperelastic solids.

The chemical nature underlying the binding affinity of a protein has been modeled using electromagnetics (EM) theory by various research groups (Figure 9). LLNL's efforts could begin by modeling the static electric field surrounding the SHAL and the protein using a 3D finite-difference or finite-element code such as the EMSolve code. The appropriate equation is the non-linear (or linearized) Poisson-Boltzman equation. In either case, the key computational bottleneck is the solution of a system of non-linear (or linearized) equations for every morphology. The Center for Applied Scientific Computing at LLNL has significant expertise on scalable multilevel algorithms for Poisson-like equations. Also, existing codes that have been developed for the ASCI program will be the starting point for a fast Poisson-Boltzman equation solver.

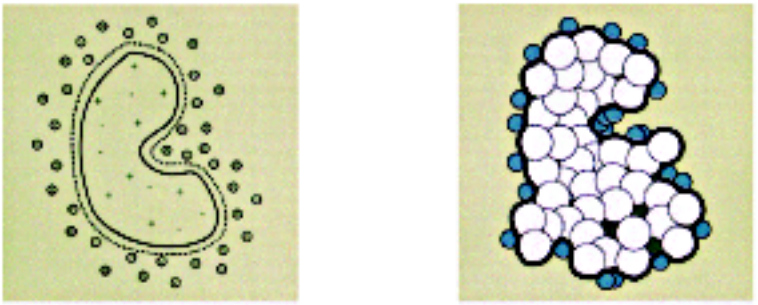

Figure 9. Published work has demonstrated the utility of continuum electromagnetics simulations for representation of electrostatic forces. Schema of a model protein-solvent system (left) and representation of dielectric assignment based on solvent accessibility (right). Ref. "The adaptive multilevel finite element solution of the Poisson-Boltzmann equation on massively parallel computers," N. A. Baker et al., IBM J. Res. & Dev. Vol. 45, No. 3/4 May/July 2001.

These electromagnetics continuum simulations take into account the morphology of the protein and treat the atoms as point charges. However, EM treatments alone will not account for the dynamic changes in the morphology of the protein (or SHAL) which is an important aspect of the problem. This is why it is necessary to run both the fluid/structure code concurrently with the electromagnetics code, as described in the next section 8.

7. Experiments for SHAL and Protein Model Development

The MD simulations performed in the PAT, CMS, and BBRP directorates will in essence provide "simulation data" for the development of the continuum models for the SHAL and protein. For example, boundary conditions can be imposed to determine the forces required to extent, twist or bend the DNA segment, thus providing information to "tune" the continuum "cable" elements. But what about real experimental data for this purpose? What specific experimental efforts will be needed to validate SHAL and Protein models, and what data will be necessary to generate?

7.1 SHAL/protein binding variables

Several variables available for optimizing the performance of SHALs will need to be studied experimentally. The SHALs currently being designed at LLNL incorporate a polyethylene glycol (PEG) polymer link between the targeting moieties on the SHAL and an additional PEG linker to a surface. The length of these PEG links will directly affect the binding properties of the SHAL to the targeted molecules. In addition, the density of tethered SHALs on the surface and the molecules that are used to dilute the surface density will have an effect on the binding properties of the SHALs to their target molecules. In addition to this, issues affecting performance include the concentration of target molecules, the flow rate of the solution containing the target molecules, the volume and geometry of the region in which the SHAL functions, and the concentrations of other molecules and ions in the solution.

7.2 Single molecule experiments

Several methods could be used to study SHAL performance and properties. The atomic force microscope (AFM) is currently being used to study the binding events between single molecules (i.e. recognition microscopy). By tethering the target molecule to the AFM tip and creating a SHAL structure on a suitable surface, many of the performance issues can be addressed. The AFM also allows other related issues like bond loading rate to be studied. To study the compressive compliance of the protein, an experiment might be performed where a monolayer of proteins is compressed between two plates while the applied force and relative displacement of the plates are measured. These "single molecule" experiments are extremely challenging, hence more effort is needed to properly scope them out.

8. "Linking" of Solid/Fluid Mechanics with Electromagnetics

After the appropriate continuum representations of the SHAL and protein are constructed using both structural/fluidics in ALE3D and electrostatic in EMSolve, a simulation of the capture of a protein by the SHAL can be performed.

The effects of the morphology of the SHAL and protein and the electrostatic nature of the attractive forces may be highly coupled (one might affect the other and vice versa). Thus it will be necessary for the fluid/structures code (ALE3D) that determines the morphology to run the problem concurrently with the EM code that solves for the attractive forces. (Of course another way to do this would be to write a new code to solve all of the PDFs simultaneously, but this would require a substantial code development effort and would not allow for short-term multiscale modeling and simulation deliverables.)

A "controller" program can be written to essentially step each code (ALE3D and EMSolve) through the problem. For example, the structure/fluid code would perform a few time-steps, and then hand off the new morphologies of the SHAL and protein to the EM code. The EM code would then be used to determine a new set of electrostatic forces that would be used to update that information in the structure/fluid code. This would proceed until the SHAL and protein were coupled; at which point the electrostatics would not be important for the coupled structure.

9. Multiscale modeling of micro/nano-cantilevers

As discussed in Section 4, the microcantilever technique has demonstrated utility for detection of a wide variety of chemical and biological agents. Also, chemically functionalized cantilevers could be mass-produced and integrated into a "sensor chip" using well-established microtechnologies. For example, one might envision an integrated sensor chip with on the order of 10^4 cantilevers capable of real-time sensing of 100s of

potential threats. Each threat would of course require a different functionalization of the beam surface. Clearly there would be a multitude of design parameters and issues in order to optimize sensitivity, manufacturing and reliability. The multiscale modeling efforts we describe here address primarily the following:

- **Beam size and geometry -** beams would need to be sized specifically for the mode of operation (static or resonant) and the size/mass of the various target agents; beam geometry would need to be designed to optimize for the mode of detection (optical or electronic)

- **Fluidic designs -** channels would need to be engineered to optimize sensing and to control sensitivity variations across large cantilever arrays

- **Multiscale materials issues -** behavior of cantilevers with dimensions of 100 microns to less than 100 nm.

The mechanics of micron and sub-micron structures, both static and dynamic response, are not fully understood and this is particularly true when these structures are immersed in a fluid medium. For example, a simple cantilever beam in a channel filled with a buffer solution has not, to our knowledge, been simulated accurately with continuum computer codes. It is believed that in-house computer codes have most of the basic capabilities needed to simulate the mechanical behavior of microcantilevers in fluids (e.g. ALE3D). Nevertheless, we are far from the kind of predictive capability needed for design, especially as the devices are further miniaturized. The bio-sensor cantilevers under development today have lengths and widths on the order of 100s of microns in order to present a large surface area but with sub-micron thickness to gain sensitivity. Even in vacuum this high aspect ratio presents a challenge to simulation, and immersion in fluid is even more demanding. Variations in the manufacturing process and ancillary surface processes such as non-specific deposition and fatigue due to stress-driven surface oxidation lead to unconventional materials properties that must be taken into account to predict both operation and failure. Surface stresses due to the captured ligands must be included. These issues become more acute as the devices are miniaturized. There is a hierarchy of material length scales from microstructural scales (e.g. grain size) to intrinsic surface layer thickness approaching the atomic scale. A robust simulation needs to be informed about these changes in physics. The overall goal of the cantilever beam multiscale modeling is to achieve and demonstrate a computer code simulation capability for high aspect ratio cantilevers in vacuum and in fluids and ranging in size from the bio-sensor microcantilevers being developed today to the ultra-small array cantilevers of the future. New physics and multiscale material models will be incorporated into in-house finite element codes as required.

The continuum model development proposed by Ian Darnell will focus on the simulation and experimental validation of a simple Si microcantilever with dimensions on the order of 10-100 micrometers, initially in vacuum. We will then move on to more challenging problems: a vibrating cantilever in a fluid, bi-material structures, and nano-size cantilevers. The nano-cantilever modeling will model cantilevers much smaller than any

proposed for bio-detection in order to provide a stringent test of the applicability of the code to a range of sizes. The nanoscale work will be highly coupled with an ER project in PAT (R. Rudd) focusing on molecular dynamics (MD) simulations of nano-structures, and the direct comparison of FEM and MD models will be very interesting. This work also ties in with AFM studies of live cells in buffer solutions in CMS by Mike McElfresh.

10. Simulation of cantilever sensing and experimental validation

The chart in Figure 10 shows the flow of modeling and experimental work ultimately leading to the simulation of a protein-detection experiment using a microcantilever beam functionalized with SHALs. As the flow chart shows, it would be necessary to have validated models for the SHAL, protein, and microcantilever (all in buffer solution) before attempting the biosensor simulation. The details of how this simulation would be carried out cannot be given at this time. However, it would utilize the same solid/fluid mechanics code, coupled with an electromagnetics code, as describe for the simple SHAL/protein experiments.

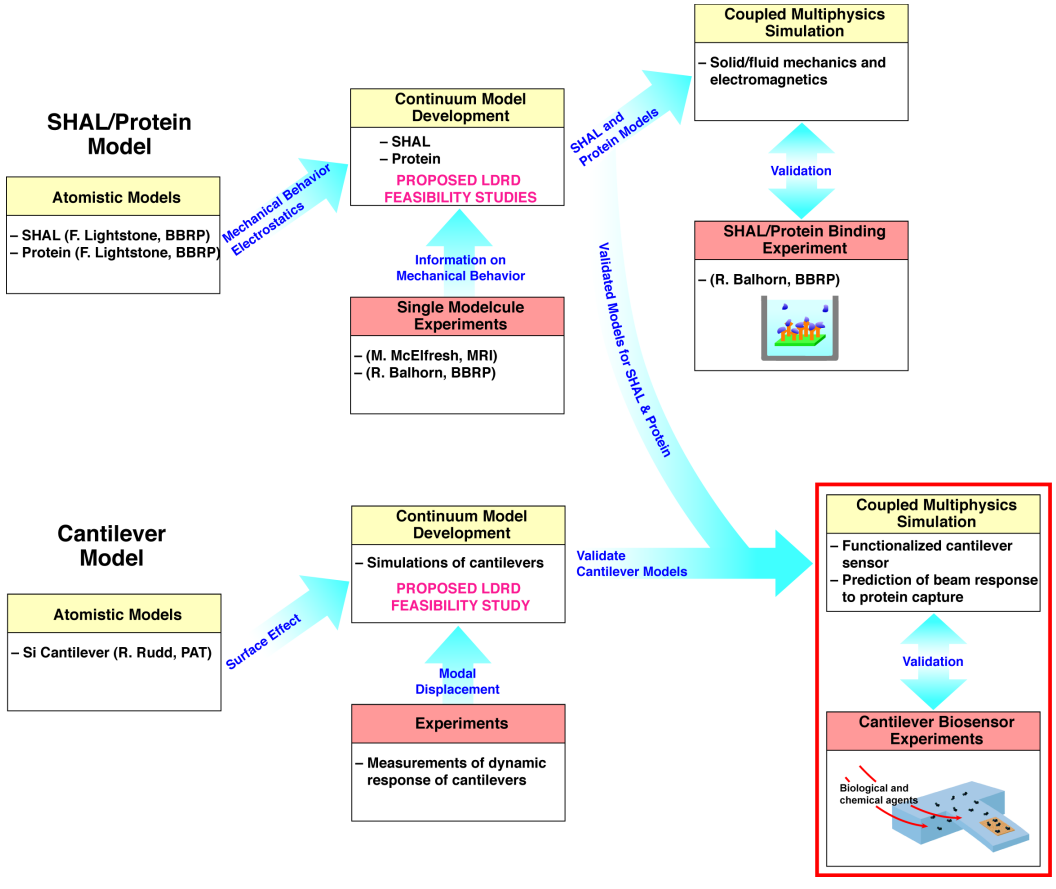

Figure 10. Road-map for modeling, experimental and simulation activities, ultimately leading to an experimentally validated simulation of a microcantilever beam biosensor. Experiments are a vital aspect of the envisioned program.

The experiments to validate a microcantilever protein-sensor would be performed using a functionalized cantilever as illustrated in Figure 3. Numerous experiments of this nature have been performed world wide and also by LLNL researchers. The well-developed experimental techniques employing microcantilevers will allow for a sound database to validate simulation results. It is envisioned that LLNL researchers would perform validation experiments involving the tetanus toxin protein and SHAL.

In addition to the on-site validation experiments, it is expected that the multiscale modeling and multiphysics simulation tools will be used to perform simulations of experiments taking place at other laboratories. Eventually all of these efforts will culminate in a multiphysics simulation capability that would be an aid in the interpretation of experiments and the developments of more effective SHALs and biosensor techniques.

11. Feasibility studies and related projects

In this white paper we have presented a road-map for the creation of a multiphysics simulation capability. To go forward with the work that is outlined, we must continue to develop a technical work plan and engage researchers – at LLNL and also at universities and other labs. For this purpose, we propose LDRD feasibility studies for FY-04 funded at a total level of approximately $250K. This will essentially be used as multidirectorate "glue" money. Critical aspects of the work needed to create a multiphysics simulation capability will be funded.

In addition, there are current research projects that could contribute to the overall goal of a multiphysics simulation capability. Some of the LDRD ER proposals that could make substantial contributions are listed here.

- **Continuum cable model**, Chris Lee, new Eng LDRD ER proposal
- **Nanomechanics,** Robert Rudd, new PAT LDRD ER proposal
- **Mechanics and Dynamics of small beams**, Ian Darnell, new Eng LDRD ER
- **Lattice Boltzman fluid/particle simulations**, D. Clague, 2nd year Eng LDRD ER
- **Probing the Properties of Cells with the Atomic Force Microscope,** Mike McElfresh, 3rd year MRI LDRD-ERI
- **Continuum modeling of Cell Membranes**, James Stolken, new Eng LDRD ER

In addition to these LDRD ER projects, there are other funding sources that could play a significant role in the overall objective, including but not limited to the following:

- **MRI university outreach minigrants**

- **BSNL research activities on microcantilever sensing techniques.**

12. Timeline and milestones

In this white paper we provide a road map for the creation of a multiphysics computer code simulation of a sensor system. Detailed technical work plans and who would do it would need to be established prior to commencing a well-coordinated and multi-directorate program. However, the following timeline is given for envisioned milestones over a three-year period.

Year 1

a. multiphysics simulation SHAL/protein binding in a static buffer solution
b. studies of a microcantilever in air and in fluid

Year 2

c. cantilever functionalized with SHAL
d. static deflection of microcantilever induced by protein capture

Year 3

e. dynamic response of micro/nano cantilever in fluid
f. change in dynamic response of mirco/nano cantilever induced by protein capture

Appendix A

The "Multiscale Modeling of Nano-scale Phenomena" white paper is the result of the work of a group of individuals at the Lab with very diverse backgrounds (biology, mechanical engineering, physics, and others). A total of 11 meetings were held over a period of 5 months to exchange information and ideas that relate to the broad areas of sensor technology, chemical and biological threats, nanomaterials, biological experiments and multiphysics computer code simulations. In general, the meetings were well attended and the following people participated at one point or another: **David Clague, Rich Couch, Rich Becker, Dan Nikkel, Scott Groves, Rob Sharpe, Mike McElfresh, Tom Slezak, Beth Vitalis, Chris Lee, Andrew J. Williamson, Robin Miles, Felice Lightstone, Kevin D. Ness, Rod Balhorn, Todd H. Weisgraber, Don Meeker, Ian Darnell, Dave Sanders, Jeffrey Florando, Monique Cosman, George Dougherty, Tim Ratto, John Rockway** and perhaps, with apologies, a few others that are not listed.

Each of the 11 meetings covered specific subjects and presentations were provided by various individuals as given below:

1. December 12, 2002; ***Dave Lassila***; Kick off meeting and general discussion of:
   - sensor mechanisms
   - types of multiscale approaches we might pursue
   - "target" sensor mechanism for the first modeling efforts
   - laboratory experiments and data to validate models and simulations
   - numerical simulation tools

2. December 19, 2002; ***Robin Miles*** and ***Beth Vitalis:*** presentations on chemical and biological threats

3. January 9, 2003; ***Dave Clague***: the "lattice Boltzmann" technique applied to fluid problems with nano-size particulates

4. January 16, 2003; ***Rich Becker***: overview of the multipyhsics capabilities of the ALE3D "finite element" computer code and surface stress implementation. ***Mike McElfresh***: discussion of experimental techniques involving micro-cantilevers

5. January 30, 2003; ***Felice Lightstone***: overview of atomistic modeling of biological molecules. ***Chris Lee***: "continuum" modeling of biological molecules

6. February 4, 2003; ***Dan Nikkel***: solid-mechanics continuum modeling of MEMs, ***Rob Rudd***: atomistic simulations of crystalline materials

7. February 27, 2003; ***Monique Cosman*** (BBRP): experimental studies on binding of synthetic high affinity ligands to target bio-molecules

8. March 13, 2003; ***Rob Sharpe***: discussion of electomagnetics simulation codes, (with some emphasis/discussion of there utility for modeling atomic bonding, electro-osmosis, electrophloresis, and surface interaction effects)

9. March 26, 2003; ***Rod Balhorn***: overview of relevant "biology experiments." The ligant/protein "binding coefficient" is of particular interest because it may be the metric of a successful multiphysics simulation of an experiment

10. April 3, 2003; ***Prof. Tonya Kuhl (UC Davis)***: "Dynamics of Grafted Polymer Chains using Biospecificity." The promoters of cell adhesion are ligands, which are often attached to semi-flexible tethers that bind to surface receptors on adjacent cells. Using a combination of Monte Carlo simulations, diffusion reaction theory, and direct experiments (surface force measurements), we have quantified polymer chain dynamics by exploiting biospecificity (ligand-receptor binding)

11. April 16, 2003; ***Prof. Andrew Cleland***, Department of Physics U.C. Santa Barbara, Title: "Integrated Nanomechanical and Nanoelectronic Structures" (**this meeting was sponsored by the MRI)**

Acknowledgements: One of the authors (DHL) would like to acknowledge the Engineering Directorate's support that was provided under the "Engineering Materials Technology" project to generate this white paper (*Jens Mahler*, acting AD). Also, *Glenn Mara, Don Meeker, Satish Kulkarni* and *Prof. Karl Pister* provided the initial direction and guidance of this work.

Special thanks to *Dr. Tomas Thundat* (ORNL) who provided information of the use of microcantilevers for sensor applications.

ENG-03-0083-NTED